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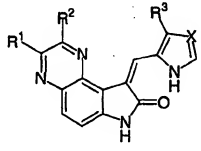
(54) Title: 4,5-PYRAZINOXINDOLES AS PROTEIN KINASE INHIBITORS



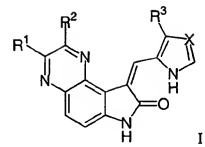
(I)

(57) Abstract

4,5-pyrazinoxindoles having formula (I), inhibit or modulate protein kinases, in particular JNK protein kinases and are useful as anti-inflammatory agents, particularly in the treatment of rheumatoid arthritis.

What Is Claimed Is:

1. A compound of formula



I

wherein:

R^1 and R^2 are independently selected from the group consisting of

hydrogen,

$-OR^4$,

$-COR^4$,

$-COOR^4$,

$-CONR^5R^6$,

$-NR^5R^6$,

lower alkyl which may be substituted by a member of the group (a) consisting of $-OR^4$, $-NR^5R^6$, halogen, $-COR^4$, $-COOR^4$, $-OCOR^4$, $-CONR^5R^6$, -CN, $-SO_2R^4$, $-SO_2NR^5R^6$; or by cycloalkyl, heterocycle, aryl, and heteroaryl, wherein the cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12};

cycloalkyl which may be substituted by a member of the group (a) a defined earlier, or by lower alkyl, heterocycle, aryl, and heteroaryl, wherein the lower alkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12};

heterocycle which may be substituted by a member of the group (a) as defined earlier, or by lower alkyl, cycloalkyl, aryl, and heteroaryl, wherein the lower alkyl and cycloalkyl each may be substituted by the group R^{11} and the aryl and heteroaryl each may be optionally substituted by the group R^{12};

aryl which may be substituted by a member of the group (b) consisting of $-OR^4$, $-NR^5R^6$, halogen, $-NO_2$, perfluoroalkyl, $-COR^4$, $-COOR^4$, $-OCOR^4$, $-CONR^5R^6$, -CN, $-SO_2R^4$, $-SO_2NR^5R^6$; or by lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl, cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

heteroaryl which may be substituted by a member of the group (b) as defined earlier, or by lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl and wherein the lower alkyl, cycloalkyl and heterocycle each may be optionally substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12}, or alternatively, R^1 and R^2 can form a ring having 5-7 atoms, said ring optionally including one or more heteroatoms and being optionally substituted by a member of the group consisting of $-OR^8$, $-COR^7$, $-COOR^7$, $-OCOR^4$, $-CONR^7R^9$, $-NR^8R^9$, or lower alkyl which may be substituted by the group R^{11};

R^3 is hydrogen, $-OR^4$, $-COR^4$, $-COOR^4$, $-OCOR^4$, $-CONR^5R^6$, halogen, -CN, perfluoroalkyl $-NR^5R^6$, or lower alkyl which may be substituted by $-OR^4$, $-OCOR^4$, or $-NR^5R^6$;

R^4 is hydrogen,

lower alkyl which may be substituted by a member of the group (c) consisting of $-OR^8$, $-COOR^7$, $-COR^7$, $-CONR^5R^6$, $-NR^5R^6$, $-SO_2R^7$, $-SO_2NR^5R^6$; or by cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

cycloalkyl which may be substituted by a member of the group (c) or by lower alkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

heterocycle which may be substituted by a member of the group (c) or by cycloalkyl, lower alkyl, aryl, and heteroaryl, and wherein the cycloalkyl and lower alkyl each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

aryl which may be substituted by a member of the group (d) consisting of $-OR^8$, $-COOR^7$, $-COR^7$, $-CONR^5R^6$, $-NR^5R^6$, $-NO_2$, halogen, perfluoroalkyl, $-SO_2R^7$, $-SO_2NR^5R^6$; or by lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl, cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12}, and

heteroaryl which may be substituted by a member of the group (d) or by cycloalkyl, lower alkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl,

cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12};

R^5 and R^6 are each independently

hydrogen,

$-COR^7$,

$-COOR^7$,

$-CONR^7R^9$,

lower alkyl which may be substituted by a member of the group (e) consisting of $-OR^8$, $-COOR^7$, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-SO_2R^7$, $-SO_2NR^7R^8$; or by cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

cycloalkyl which may be substituted by a member of the group (e) as defined earlier, or by lower alkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

heterocycle which may be substituted by a member of the group (e) as defined earlier, or by cycloalkyl, lower alkyl, aryl, and heteroaryl, and wherein the cycloalkyl and lower alkyl each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12},

aryl which may be substituted by a member of the group (f) consisting of OR^8, $-COOR^7$, $-COR^7$, $-CONR^7R^8$, $-NR^7R^8$, $-NO_2$, halogen, perfluoroalkyl, $-SO_2R^7$, $-SO_2NR^7R^8$; or by lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl, cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12}, and

heteroaryl which may be substituted by a member of the group (f) as defined earlier, or by lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, and wherein the lower alkyl, cycloalkyl and heterocycle each may be substituted by the group R^{11} and the aryl and heteroaryl each may be substituted by the group R^{12}; or alternatively, $-NR^5R^6$ can form a ring having 3 to 7 atoms, said ring optionally including one or more additional hetero atoms and being optionally substituted by lower alkyl, $-OR^8$, $-COR^7$, $-COOR^7$, $-CONR^7R^9$, or $-NR^8R^9$;

R^7 is hydrogen or lower alkyl which may be substituted by a member of the group consisting of cycloalkyl, heterocycle, aryl, heteroaryl, $-OR^9$, or $-NR^8R^9$;

R^8 is hydrogen, $-COR^9$, $-CONR^{10}R^9$, or lower alkyl which may be substituted by R^{11};

R^9 and R^{10} are each independently hydrogen or lower alkyl;

R^{11} is $-OR^9$, $-COR^9$, $-COOR^9$, $-OCOR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-N(COR^9)R^{10}$, $-SO_2R^9$, or $-SO_2NR^9R^{10}$;

R^{12} is $-OR^9$, $-COR^9$, $-COOR^9$, $-OCOR^9$, $-CONR^9R^{10}$, $-NR^9R^{10}$, $-N(COR^9)R^{10}$, $-SO_2R^9$, $-SO_2NR^9R^{10}$, halogen, $-CN$, $-NO_2$, or perfluoroalkyl; and

X is -N- or -C-.

and prodrugs and pharmaceutically active metabolites of compounds of Formula I; and the pharmaceutically acceptable salts of the foregoing compounds.

2. A compound of claim 1, wherein

R^1 and R^2 are independently

hydrogen,

$-NR^5R^6$,

lower alkyl which may be substituted by R^{11}, cycloalkyl, heterocycle, aryl and heteroaryl, wherein the cycloalkyl and heterocycle may be substituted by R^{11}, and the aryl and heteroaryl may be substituted by R^{12};

cycloalkyl which may be substituted by R^{11}, lower alkyl, heterocycle, aryl and heteroaryl, wherein the lower alkyl and heterocycle may be substituted by R^{11}, and the aryl and heteroaryl may be substituted by R^{12};

heterocycle which may be substituted by R^{11}, lower alkyl, cycloalkyl, aryl and heteroaryl, wherein the lower alkyl and cycloalkyl may be substituted by R^{11}, and the aryl and heteroaryl may be substituted by R^{12};

aryl which may be substituted by R^{12}, lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, wherein the lower alkyl, heterocycle and cycloalkyl may be substituted by R^{11}, and the aryl and heteroaryl may be substituted by R^{12};

heteroaryl which may be substituted by R^{12}, lower alkyl, cycloalkyl, heterocycle, aryl, and heteroaryl, wherein the lower alkyl, cycloalkyl and heterocycle may be substituted by R^{11}, and the aryl and heteroaryl may be substituted by R^{12}; or alternatively,

R^1 and R^2 may form a ring having 5 to 7 atoms and optionally being substituted by the group consisting of $-OR^8$, $-COR^7$, $-COOR^7$, $-CONR^7R^9$, $-NR^8R^9$, and lower alkyl which may be substituted by R^{11}.

3. The compound of claim 2 wherein R^3 is hydrogen, $-OR^4$, $-NR^5R^6$, or lower alkyl which may be substituted by the group consisting of $-OR^4$ and $-NR^5R^6$.

4. The compound of claim 2 wherein R^3 is hydrogen, $-OR^9$, or lower alkyl which may be substituted by the group consisting of $-OR^9$ and $-NR^9R^{10}$.

5. The compound of claim 1, which is (Z)-7,9-Dihydro-2,3-dimethyl-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-8H-pyrrolo-[3,2-f]quinoxalin-8-one

6. The compound of claim 1, which is (Z)-3-Butyl-7,9-dihydro-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-methyl-8H-pyrrolo[3,2-f]quinoxalin-8-one

7. The compound of claim 1, which is (Z)-2-butyl-7,9-dihydro-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-3-methyl-8H-pyrrolo[3,2-f]quinoxalin-8-one

8. The compound of claim 1, which is (Z)-7,9-Dihydro-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2-methyl-3-phenyl-8H-pyrrolo[3,2-f]quinoxalin-8-one

9. The compound of claim 1, which is (Z)-7,9-dihydro-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-3-methyl-2-phenyl-8H-pyrrolo[3,2-f]quinoxalin-8-one

10. The compound of claim 1, which is (Z)-7,9-Dihydro-2,3-di-(2-furanyl)-9-[(3-methoxy-1H-pyrrol-2-yl)methylene]-8H-pyrrolo[3,2-f]quinoxalin-8-one

11. The compound of claim 1, which is (Z)-1,3,5,6,7,8-Hexahydro-3-[(3-methoxy-1H-pyrrol-2-yl)methylene]-2H-pyrrolo[3,2-a]phenazin-2-one

12. A pharmaceutical composition comprising as an active ingredient a compound of any one of claims 1 to 11 and a pharmaceutically acceptable carrier or excipient.

13. A compound of any one of claims 1 to 11 for use as a medicament, particularly for the treatment and/or control of inflammation and neurodegenerative diseases, particularly rheumatoid arthritis, or for treating solid tumors, in particular breast or colon tumors.

14. The use of a compound of formula I or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 11 in the preparation of a medicament containg such compound for the treatment and/or control of inflammation and neurodegenerative diseases, particularly rheumatoid arthritis, or for treating solid tumors, in particular breast or colon tumors

15. The invention as described hereinbefore.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/09806

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D487/04 A61K31/50 A61K31/41 A61P29/00
//(C07D487/04,233:00,241:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,Y	WO 99 15500 A (GLAXO GROUP LTD.) 1 April 1999 (1999-04-01) claims 1-26	1-15
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Y	WO 98 07695 A (SUGEN, INC.) 26 February 1998 (1998-02-26) cited in the application claims 1-12	1-15

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
6 April 2000	14/04/2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/09806

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 99/09806

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